Opposing microRNA families regulate self-renewal in mouse embryonic stem cells.

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Public Summary:
MicroRNAs are short RNA molecules that do not encode for proteins but rather regulate the production of proteins from messenger RNAs. Importantly, microRNAs have been implicated in a broad range of stem cell roles in both healthy and diseased tissues. MicroRNAs show great promise as both biomarkers and therapeutics for disease. Here, we describe how miRNA regulate the decision a embryonic stem cell has to make with every cell division - make another copy of itself of differentiate into specialized tissues. In particular, we describe two microRNA families: one that promotes self-renewal and another that promotes differentiation. Having uncovered these roles for the microRNAs enables us to translate this knowledge in order to manipulate embryonic stem cells to our advantage - expand or produce adult tissues. Furthermore, having uncovered the targets of these microRNAs, we can begin to think about drugs that could have similar effects.

Scientific Abstract:
When embryonic stem cells (ESCs) differentiate, they must both silence the ESC self-renewal program and activate new tissue-specific programs. In the absence of DGCR8 (Dgcr8(-/-)), a protein required for microRNA (miRNA) biogenesis, mouse ESCs are unable to silence self-renewal. Here we show that the introduction of let-7 miRNAs-a family of miRNAs highly expressed in somatic cells-can suppress self-renewal in Dgcr8(-/-) but not wild-type ESCs. Introduction of ESC cell cycle regulating (ESCC) miRNAs into the Dgcr8(-/-) ESCs blocks the capacity of let-7 to suppress self-renewal. Profiling and bioinformatic analyses show that let-7 inhibits whereas ESCC miRNAs indirectly activate numerous self-renewal genes. Furthermore, inhibition of the let-7 family promotes de-differentiation of somatic cells to induced pluripotent stem cells. Together, these findings show how the ESCC and let-7 miRNAs act through common pathways to alternatively stabilize the self-renewing versus differentiated cell fates.